MS02-1-4 Structure of the diabetogenic I-Ag7 receptor with a bound hybrid insulin peptide
#MS02-1-4

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Abstract
The NY4.1 T cell clone was originally isolated from pancreatic islet-infiltrating lymphocytes from nonobese diabetic (NOD) mice[1]. Recently, evidence was provided for promiscuous recognition of several different hybrid insulin peptides (HIPs) by the highly diabetogenic, I-Ag7-restricted 4.1-T cell receptor (TCR)[2]. In TCR-transgenic NOD mice, recognition of these peptide-MHCII complexes triggers the activation and recruitment of 4.1-CD4+ T cells into pancreatic islets, leading to rapid destruction of pancreatic beta cells and over type 1 diabetes within the first few weeks of life.
To understand, at an atomic level, how this diabetogenic receptor binds HIP antigens, I solved the crystal structure of an agonistic HIP/I-Ag7 complex at 1.8 Å resolution.
The HIP39 epitope is tightly packaged into the peptide-binding groove of the MHCII molecule through a nourished net of interactions with both the I-Aad and I-Abg7. These include Van der Waals (VDW), hydrogen bonding (H-bonds), ionic interactions (salt bridges) and water bridges. Positions P5, P7 and P8 in the peptide are occupied by acidic residues (Glu/Glu/Asp) that expose side chains outwardly, making them available for potential interactions with cognate TCRs. Importantly, these acidic residues and positions are highly abundant in HIPs derived from a human lymphoblastoid cell line[3].
Altogether, this crystal structure provides high-resolution data that enable an accurate definition of the HIP/I-Ag7 binding signature and contribute to a better understanding on how HIP antigens bind diabetogenic receptors. These complexes are known to trigger T cell autoreactivity to self tissues in type I diabetes.

References
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Structure of the 4.1-TCR:HIP39/I-Ag7 complex